

Novel postoperative adjuvant strategy prevents early hepatic recurrence after resection of pancreatic cancer

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Abstract

Background/Purpose It has been reported recently that adjuvant gemcitabine prolonged postoperative disease-free survival in patients with resectable pancreatic cancer. However, the efficacy was limited and further studies are required to improve the prognosis. In particular, postoperative hepatic recurrence often occurs even after gemcitabine treatment.

Methods We are currently trying to evaluate the efficacy of postoperative combination therapy of high-dose 5-fluorouracil (5-FU) arterial infusion with systemic gemcitabine. Patients received weekly high-dose 5-FU through the hepatic artery using a port-catheter system (1000 mg/m² for 5 h) plus concurrent systemic gemcitabine (1000 mg/m²).

Results Thirty-one patients were enrolled and 29 patients (94%) completed the scheduled adjuvant chemotherapy. The toxicity was acceptable and this regimen was well feasible as an outpatient treatment. At the time of analysis, 21 patients (68%) had recurrence. Local recurrence was most frequently observed, in 43% of the patients with recurrence. On the other hand, hepatic recurrence developed in only 2 patients (10%). The 1-year disease-free rate and overall survival rate were 62.9 and 100%, respectively.

Conclusion Our novel adjuvant strategy had a significant beneficial effect on early hepatic recurrence and may have the potential to prolong the overall survival of pancreatic cancer patients.

Keywords Pancreatic cancer · Hepatic recurrence · Surgery · Chemotherapy · Gemcitabine

Introduction

Pancreatic cancer remains a challenge to clinicians, because the prognosis is still extremely poor [1]. Although only surgery offers a hope of complete cure, a number of patients often develop early recurrence even after curative-intent surgery [2–4]. Currently, gemcitabine is widely used as a standard systemic chemotherapy for unresectable pancreatic cancer [5, 6]. Furthermore, two recent randomized controlled trials (RCTs), both phase III, from Europe [Charité ONKOlogie Clinical Studies in GI cancer (CONKO-001)] and Japan [Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer (JSAP-02)], have successfully demonstrated similar results, in that the use of gemcitabine as adjuvant chemotherapy significantly delayed postoperative recurrence [7, 8]. However, the clinical efficacy of adjuvant gemcitabine is limited and the patient prognosis remains unsatisfactory. Therefore, a new therapeutic strategy needs to be established to improve the prognosis of pancreatic cancer patients.

It is well recognized that the most common site of recurrence after curative resection for pancreatic cancer is the liver [3, 9–14]. In particular, hepatic recurrence often develops early in the postoperative period and becomes a direct cause of early death [13–16]. The two RCTs of adjuvant gemcitabine treatment cited above have reported

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that approximately one-third of the initial recurrence was liver metastasis [7, 8]. Importantly, the incidence of liver metastasis as the initial recurrence did not differ between the gemcitabine and control groups in both these RCTs [7, 8]. Thus, in order to further prolong the patient prognosis, early postoperative hepatic recurrence is clearly a critical issue that needs to be overcome.

We are currently trying to establish a new postoperative strategy to prevent hepatic recurrence and prolong patient survival after pancreatic resection for pancreatic cancer. To this end, we have employed hepatic arterial chemoinfusion (HAI) of high-dose 5-fluorouracil (5-FU) combined with systemic infusion of gemcitabine. In this study, we evaluated the effect of this combination therapy, in an adjuvant setting, on early recurrence.

Patients and methods

Between March 2006 and March 2009, 31 patients who underwent macroscopically curative resection of pancreatic cancer were enrolled in the study. Patients were not eligible for this study if they had other concomitant malignant diseases, active infection, history of any preoperative anticancer therapies, positive peritoneal cytology during surgery, distant metastasis (except for distant lymph node metastasis confirmed by a resected specimen), clinically significant pleural effusions, or any serious systemic disorders. All patients provided written informed consent before study enrollment according to the rules and regulations of our institution. When the patients had recovered from surgery and were pathologically diagnosed as having invasive ductal adenocarcinoma of the pancreas, a port-catheter system for HAI was installed by experienced interventional radiologists, as previously reported [17, 18]. In brief, an anticoagulant-coated tapered 5F indwelling catheter with a manually made side hole (Anthon PU catheter; Toray Medical, Tokyo, Japan; or W-Spiral catheter; Piolax Medical Devices, Tokyo, Japan) was inserted from the femoral artery. In patients with a distal pancreatectomy, the catheter tip was introduced into the gastroduodenal artery with fixation using metallic coils (Tornado; Cook, Bloomington, IL, USA) and the side hole was positioned in the common hepatic artery. In patients with pancreaticoduodenectomy or total pancreatectomy, the catheter tip was introduced deeply into the right or left hepatic artery and the side hole was positioned in the proper or common hepatic artery. The proximal end of the catheter was connected to an implanted port (Celsite Port; Toray Medical) that would be embedded subcutaneously. To achieve maximum efficacy of the HAI chemotherapy while avoiding adverse effects, the unification of hepatic artery blood supply was attempted as described previously [18]. Blood supply alteration was performed in 9 patients (29%).

The postoperative chemotherapy regimen consisted of weekly HAI of high-dose 5-FU and systemic infusion of gemcitabine. Patients received 6 cycles of gemcitabine every 4 weeks. Each cycle consisted of 3 weekly infusions of gemcitabine 1000 mg/m² given by intravenous infusion for 30 min, followed by a 1-week pause. In the first 3 cycles, concomitant 5-FU 1000 mg/m² was given by HAI for 5 h. For the 5-h HAI, a portable pump (DOSI-FUSER; Leventon, Barcelona, Spain) was used. To confirm the proper condition of the port-catheter system, drug distribution into the whole liver, and the condition of the hepatic artery and liver, computed tomography and angiography via a reservoir system were performed after each cycle of HAI. The catheter management and HAI were performed by interventional radiologists in close communication with surgeons. After the patients' completion of the HAI, computed tomography was performed every 2–3 months to assess postoperative recurrence.

Adverse events were assessed according to the Common Toxicity Criteria of the National Cancer Institute (version 3.0). Stage classification and the evaluation of resected specimens were performed according to the sixth edition of the TNM classification system of the International Union against Cancer. Survival estimates were calculated by the Kaplan–Meier method.

Results

Patient characteristics

Thirty-one patients were pathologically diagnosed with invasive pancreatic adenocarcinoma (Table 1). Eight patients (26%) had a microscopically positive margin (R1). Eighty-three percent of the patients were classified as stage IIA or IIB. Three stage IV patients with paraaortic lymph node metastasis were also treated with this protocol. Nodal involvement was identified in 61% of the patients. The median follow-up period was 20.5 months (range 6.0–45.4 months). Twenty-nine patients (94%) were followed up for more than 1 year after surgery.

Toxicity

The regimen was well tolerated and feasible as an outpatient treatment. A total of 26 patients (84%) experienced any grade 3 or 4 toxicities. The details of major toxicities observed during the treatment are shown in Table 2. The incidence of grade 3 and 4 adverse events seemed to be almost equal to that in one of the previous reports on adjuvant gemcitabine [8]. Although severe leukopenia and neutropenia were frequently observed, the patients recovered promptly without complications after 1-week pause in

Table 1 Patient characteristics

Characteristics	
Age (years)	63.5 (range 33–80)
Gender (male/female)	19/12
Operative procedures	
Pancreatoduodenectomy	20 (64%)
Distal pancreatectomy	9 (29%)
Total pancreatectomy	2 (7%)
Resection status	
R0	23 (74%)
R1	8 (26%)
Pathological stage	
IB	2 (7%)
IIA	10 (32%)
IIB	16 (51%)
IV	3 (10%)
Tumor status	
T2	3 (10%)
T3	28 (90%)
Nodal status	
N0	12 (39%)
N1	19 (61%)
Histological grade	
1/2/3/4	16/13/1/1

Table 2 Grade 3 and 4 adverse events

Toxicity	Grade 3	Grade 4
Nonhematologic		
Diarrhea	0 (0%)	0 (0%)
AST/ALT	0 (0%)	0 (0%)
Liver abscess	1 (3%)	0 (0%)
Hematologic		
Leukopenia	9 (29%)	0 (0%)
Neutropenia	12 (39%)	9 (29%)
Anemia	4 (13%)	0 (0%)
Thrombocytopenia	3 (10%)	2 (6%)

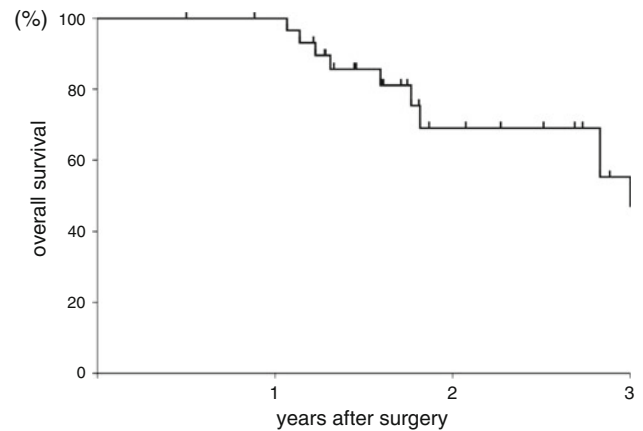
AST Aspartate aminotransferase, ALT alanine aminotransferase

the treatment. Grade 2 liver dysfunction (aspartate aminotransferase [AST]/alanine aminotransferase [ALT] elevation) was found in 7 patients (23%). Liver abscess developed in only one patient during the treatment. She was conservatively treated and completely cured. She received all adjuvant treatments thereafter. Twenty-nine patients completed the scheduled adjuvant chemotherapy. Of the other two patients, one refused to continue with the adjuvant chemotherapy after 7 doses of treatment, due to diarrhea that seemed to be related to nerve dissection. The other patient developed peritoneal metastasis with massive

Table 3 Patterns of initial recurrence

	No.	Percentage	Time to recurrence ^a
Liver	2	10	11.5
Local	9	43	8.4
Lung	6	29	13.3
Peritoneum	3	14	14.8
Other	8	38	14.6

^a Median time to recurrence from surgery (months)

**Fig. 1** Overall survival of 31 pancreatic cancer patients treated with weekly high-dose 5-fluorouracil (5-FU) through the hepatic artery plus concurrent systemic gemcitabine

ascites after 4 doses; the treatment was switched to systemic chemotherapy with gemcitabine and S-1. These two patients were included for further analysis.

Postoperative survival and recurrence patterns

At the time of analysis, 21 patients (68%) had recurrence (Table 3). The most frequent site of initial recurrence was local, in 43% of the patients with recurrence, followed by the lung in 24%. The median time to recurrence was 8.4 months for local relapse and 13.3 months for lung metastasis. On the other hand, hepatic recurrence was identified in only 2 patients (10%) and the time to metastasis was 11.5 months. The 1-year disease-free and overall survival rates were 62.9 and 100%, respectively, while the estimated median disease-free and overall survivals were 14.8 and 37.7 months, respectively. The estimated overall survival rates were 100% at 1 year, 69% at 2 years, and 55% at 3 years (Fig. 1).

Discussion

Liver metastasis after surgical resection for pancreatic cancer is the most frequent pattern of distant recurrence. To

prevent hepatic recurrence, a number of clinical studies have investigated treatments including radiotherapy and chemotherapy. However, to date, a definitive therapeutic strategy has not been established. Liver perfusion chemotherapy (LPC) may be a promising strategy and has been performed by several groups [19–25], with LPC being carried out via the hepatic artery or portal vein, or both. The authors of some of these studies claimed that LPC prevented hepatic recurrence and prolonged patient survival. However, LPC has not been universally accepted as adjuvant treatment for pancreatic cancer. This may be because of its complicated surgical procedure and the requirement for careful perioperative management [21]. Furthermore, because only a few prospective studies with small numbers of patients have been reported, there is no convincing clinical evidence of an overall survival advantage of LPC [20, 21]. There are several advantages of our treatment protocol. First, the regimen was well feasible as an outpatient treatment. Patients were usually requested to come to the hospital only once a week. Second, toxicities were mild and general adverse effects were similar to those experienced with the adjuvant treatment of gemcitabine alone [7, 8]. Third, because the HAI was initiated when patients had fully recovered from the surgery and because the procedure was entirely performed by experienced interventional radiologists, it did not require any surgical manipulations. However, complications related to HAI can occur, especially the development of liver abscess, and caution needs to be exercised if an abscess develops, because it sometimes requires invasive drainage and this causes a long delay in the continuation of adjuvant chemotherapy. Therefore, we always paid attention to the condition of the liver and hepatic arteries, as well as the catheter system, by checking computed tomography and angiography via the reservoir system after each cycle of HAI. Importantly, a close relationship between surgeons and interventional radiologists and close communication between them is critical for a successful outcome with minimal complications.

To achieve long-term survival after surgical resection for pancreatic cancer, both local recurrence and distant metastasis need to be controlled. In general, distant recurrence is usually caused by hematogenous metastasis, while local recurrence may be a result of infiltrative invasion by the primary tumor or lymphatic metastasis [12–14]. Some authors have reported that the survival of patients with liver metastasis was shorter than that of patients with local recurrence [12, 13]. Furthermore, an autopsy study by Hishinuma et al. [16] has suggested that the direct cause of death after potentially curative resection of pancreatic cancer was distant metastasis rather than local recurrence. On the other hand, Tani et al. [14] have recently reported that liver metastasis as an initial site of recurrence did not

influence the overall patient survival. In fact, because many patients have both local and distant recurrences, regional therapy including LPC may be not sufficient to prevent these two recurrence patterns. Thus, our treatment strategy may be theoretically reasonable, because it consisted of systemic chemotherapy with intensive regional chemotherapy targeting the most frequent recurrence site, i.e., the liver.

The similar results from two RCTs might demonstrate that adjuvant therapy can improve postoperative patient survival. Compared with the results of the CONKO-001 and JSAP-02 trials, the beneficial effect of our treatment on postoperative early recurrence appears to be greater (Table 4) [7, 8]. In particular, initial hepatic recurrence was markedly prevented, thereby possibly resulting in a 1-year survival of 100%. Of note, a recent study using LPC with 5-FU followed by systemic gemcitabine has shown a hepatic recurrence rate of 25.9% and a 1-year overall survival rate of 81.5% [21]. There may be several reasons why our treatment had a better impact on early postoperative outcome than that study. First, we used high-dose 5-FU for HAI. The total amount of 5-FU was approximately 13500 mg, given in 9 doses; this was much more than the total amount used with previous treatment protocols [21–26]. Second, we used weekly 5-h infusion for HAI. Thus, in comparison with low-dose continuous infusion for several weeks, an extremely high concentration of 5-FU in the liver could have been achieved, thereby leading to the death of occult micrometastatic tumor cells. Third, the concomitant use of gemcitabine with 5-FU may have induced a synergistic antitumor effect. In fact, both basic and clinical studies have shown synergistic interaction between 5-FU and gemcitabine [27, 28]. Although the underlying mechanisms may be complex, there are several possible explanations for this possible synergism. Thymidylate synthase inhibitors such as 5-FU increase nucleotide transporters, thereby resulting in augmentation of the cellular uptake of gemcitabine. On the other hand, gemcitabine also enhances 5-FU activity through the inhibition of deoxycytidine kinase and ribonucleotide reductase, a key

Table 4 Comparison of efficacy in terms of postoperative early recurrence

	Present study	CONKO-001 [7]	JSAP-02 [8]
Number of patients	31	179	58
Initial hepatic recurrence (%)	10	36	30
1-year DFS rate (%)	63	58	49
1-year OS rate (%)	100	73	78

CONKO-001 Charité ONKOlogie Clinical Studies in GI cancer, JSAP-02 Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer, DFS disease-free survival, OS overall survival

enzyme in the salvage pathway of pyrimidine biosynthesis. These mechanisms are not mutually exclusive. To our knowledge, this is the first study to evaluate the combination of systemic gemcitabine with high-dose 5-FU for HAI as adjuvant treatment for pancreatic cancer.

In conclusion, our new postoperative adjuvant strategy had a significant effect on the prevention of early hepatic recurrence after pancreatic resection for pancreatic cancer. To confirm the therapeutic efficacy of this regimen, long-term follow-up and careful analysis of this study will be crucial. Furthermore, a large-scale prospective study may be required to prove the regimen's overall survival advantage.

Discussion at the plenary session of the 22nd Congress of the Japanese Society of Hepato-Biliary-Pancreatic Surgery, 27 May 2010

Comments by K. Yamaguchi

What was the completion rate for the treatment? How many patients were required for dose reduction of the chemotherapy? How did you treat patients who had developed postoperative recurrence after completion of the adjuvant chemotherapy?

Answer by M. Sho

Twenty-nine out of 31 patients completed the scheduled adjuvant chemotherapy. One patient refused the continuation of the treatment due to postoperative diarrhea. The other patient developed peritoneal recurrence during the treatment. Therefore, the treatment was switched to systemic chemotherapy. The treatment sometimes had to be postponed, mainly due to hematological toxicity. However, none of the patients needed dose reduction. When the recurrence had developed more than 6 months after the completion of the adjuvant therapy, gemcitabine was given again. If the patients had recurrence within 6 months after the adjuvant therapy, S-1 was applied.

Comments by K. Aiura

Were there any unique characteristics in the two patients who developed liver metastases as the initial recurrence? In your series, have you experienced any cases in which elevated preoperative carbohydrate antigen 19-9 (CA19-9) had not returned to normal before starting adjuvant therapy? In those cases, did the CA19-9 level decrease during adjuvant therapy? The rate of postoperative pulmonary recurrence seems relatively high. Do you think that the incidence was related to the inhibition of hepatic

recurrence by the adjuvant therapy? What do you think about the continuation of your adjuvant treatment for a longer time than planned?

Answer by M. Sho

There were no specific clinical and pathological characteristics in those two patients. In a few cases, the elevated serum CA19-9 level before initiating adjuvant therapy decreased to normal during the postoperative treatment. It is possible that pulmonary metastasis as the initial recurrence was found relatively more often because of the inhibition of hepatic recurrence. However, the pulmonary recurrence was usually found relatively later after surgery and in some cases was successfully treated with the subsequent chemotherapy using S-1 or other combination chemotherapies. I think that adjuvant chemotherapy should be limited to a certain postoperative period, since a few patients might be completely cured by surgery alone and postoperative chemotherapy may be harmful.

Comments by S. Satoi

The completion rate of adjuvant therapy seems high in your series compared to previous reports of the use of adjuvant gemcitabine treatment. What do you think is the reason? It seems that local recurrence should be the next target to further improve patient survival. Are there any future plans or ongoing studies to prevent local recurrence?

Answer by M. Sho

It may be because we started the treatment when patients had fully recovered. And we properly skipped chemotherapy based on myelosuppression or the patient's condition. In addition, we routinely used cepharanthine to prevent leukopenia due to chemotherapy. However, I'm not sure about the exact reason why we could complete the scheduled adjuvant therapy in most cases. To prevent local recurrence, we are currently trying to establish a new approach using neoadjuvant chemoradiotherapy followed by curative-intent surgery and this adjuvant therapy.

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